DETAILED ACTION

New Claims 65-67 are pending in the instant application. Claims 1-64 are canceled.

Response to Non-Final Office Action

Acknowledgment is made of applicant's response and amendment of the claims filed on 4/16/2010.

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Claims 28-31 were rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, wherein the instantly claimed compounds are directed to methods of treating a metabolic-related disorder and raising HDL comprising administering to an individual in need of such treatment a therapeutically effective amount of a compound of claim 4. New claim 67 is drawn to:

> 67. (New) A method of lowering free fatty acids in an individual comprising administering to said individual a therapeutically-effective amount of 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydro-cyclopentapyrazole, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

Applicants response has been carefully considered, but is not found persuasive. Applicants argue that 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole can lower free fatty acids because (1) the EC50 data in the nicotinic acid binding competition assay and (2) the Phase I and II clinical trial data in the Semple and Lai references.

The issue is with the term “lowering free fatty acids.” It is a broad term that has been linked to many different disorders. This assertion is based on the definition of “lowering free fatty acids” found in the background of the instant specification. The specification states that "high levels of plasma free fatty acids are associated with insulin resistance and type 2 diabetes." See instant specification page 1. “The consequence of decreasing plasma free fatty acids is two-fold. First, it will ultimately lower LDL-cholesterol and raise HDL-cholesterol levels, independent risk factors, thereby reducing the risk of mortality due to cardiovascular incidence subsequent to atheroma formation. Second, it will provide an increase in insulin sensitivity in individuals with insulin resistance or type 2 diabetes. Unfortunately, the use of nicotinic acid as a therapeutic is partially limited by a number of associated, adverse side-effects. These include flushing, free fatty acid rebound, and liver toxicity.” See instant specification page 2. Based on the definition of “lowering free fatty acid” from the instant specification it appears that “lowering free fatty acid” is a broad term and there are several consequences depending on the patient population being tested, i.e. lowering LDL-cholesterol levels, raising HDL-cholestrol levels, treating cardiovascular disorders, treating insulin resistance, treating type 2 diabetes, etc... Based on the definition provided in the instant specification, the term “lowering free fatty acids” is considered broad because of the wide range of disorders that can be treated.

The EC50 data in the nicotinic acid binding competition assay was fully considered. However, the issue was that the nexus between the data and the method of lowering free fatty acids could not be ascertained. The nicotinc acid binding

competition assay appears to demonstrate that the instantly claimed compounds are partial nicotinic acid receptor agonists. Support for a nicotinic acid receptor agonist in lowering free fatty acids in general is unclear.

The Phase I and II clinical trial data has been considered fully, but is not found persuasive for a method of lowering free fatty acid alone. The Semple and Lai references studied lowering free fatty acids. The references showed that 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole was found to lower plasma free fatty acids by activation of GPR109a, which would result in similar "HDL-c elevating lowering effect observed with nicotinic acid" in patients with specific disorders. See Semple page 5104, column 2 and Lai page 376, column 2. The studies linked lowering free fatty acids with a particular disorder, such as dyslipidemia, but not the treatment of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or triglycerides. See Semple page 5101, Abstract and Lai, page 376, column 1. It is noted that the free fatty acid lowering response of 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole was not evaluated in phase II clinical trials. See Lai, page 382, column 1, paragraph 1. Based on the studies of Stemple and Lai it appear that the lowering of free fatty acids has been connected to disorders such as dyslipidemia, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or triglycerides and that 3-(1H-tetrazol-5-yl)-2,4,5,6-tetrahydrocyclopentapyrazole has shown promise in the lowering of free fatty acids connected to dyslipidemia, but not high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or triglycerides. Therefore, it is asserted that lowering free fatty acids should be associated with a particular disorder and patient population to be

treated. The term lowering free fatty acids alone is broad and a specific patient population cannot be ascertained from that description alone. Therefore, claim 67 directed to lowering free fatty acid is rejected as not enabled.

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Claims 4, 7, 10, 11, 14, 17-22, 26-28, 31 and 41 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for compounds and compositions of claim 4, does not reasonably provide support for solvates or hydrates of those compounds. New claims 65-67 contain the terms "solvate" and "hydrate."

Applicants arguments have been carefully considered, but are not found persuasive. Applicants argue that the presentation given at the Office cannot be used to support an enablement rejection because of the date of the presentation. The presentation given by the office summarized what is known by one of ordinary skill in the art. Even if the presentation is not considered, the terms solvates and hydrates are not enabled. Applicants cite the *Borkowski* and *Atlas Powder* cases and these cases are acknowledged, but Examiner believes that the facts of the *Morton International* case are more on point because the examples and procedures in the instant specification fail to produce a solvate or hydrate.

Solvates and hydrates cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ 2d 1190, "the specification purports to teach, with over fifty examples, the preparation of the claimed compounds

with the required connectivity. However…there is no evidence that such compounds exist…the examples of the `881 patent do not produce the postulated compounds…there is…no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates or hydrates of the instantly claimed compounds exist. If they did, they would have been formed. Hence, applications must show that solvates and hydrates can be made, or limit the claims accordingly by deleting the terms solvates and hydrates.

It is not the norm that one can predict with any accuracy a particular solvate form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing in vivo. The specification provides no guidance as to what types are suitable for the instantly claimed compounds. Therefore, claims 65-67 are rejected because the instant disclosure does not provide support for the terms "solvate" or "hydrate." Please see Office Action mail date 10/19/2009, pages 4-6 for additional information.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Susannah Chung/
Examiner, Art Unit 1626